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Hemodynamic analysis based on biofluid models and MRI velocity measurements

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Chapter 1

Introduction

1.1 Clinical motivation

Cardiovascular disease (CVD) is the major cause of death globally [WHO18]. Alone in Europe, CVD causes 3.9 million deaths per year, accounting for 45 % of deaths from all causes. The estimated overall cost of CVD for the economy of the European Union is €210 billion [Wil+17].

CVD comprises many different diseases, the most common being coronary heart disease. The risk factors of CVD are numerous, including diet, lifestyle and genetics, and are in many cases avoidable [MMG08]. A subset of CVD is congenital heart disease (CHD), i.e., anomalies of the heart or the great vessels in close proximity to the heart present at birth, the cause of approximately 303 300 deaths per year globally [GBD16].

One example of CHD is coarctation of the aorta (CoA), a complex disease of the vasculature in which a stenosis or long narrowed segment in the aorta, typically located at the *ductus arteriosus* insertion, obstructs the blood flow and imposes significant afterload on the left heart ventricle [Bau+10]. CoA accounts for 5 % to 8 % of all CHD, with a prevalence of 3 in 10 000 live births [Erb+14]. If untreated, 80 % of patients CoA die from complications associated with the disease [Hir+10].

CVDs generally affect and alter the blood circulation and the hemodynamic flow patterns in the heart or blood vessels. This can occur for instance by redirection or obstruction of the blood flow due to malformations of the heart, vessels or heart valves, or by alteration of the tissue properties (e.g., stiffness, lesions) or due to plaques. For instance, valvular stenosis and narrowing of vessels due to CoA or atherosclerosis can cause oscillatory flow disturbances and turbulence [Ku97], lead to a drop in hemodynamic pressure and thus an increased cardiac load. Disturbances in the flow patterns on the other hand can cause or contribute to the progression of CVDs [RE06; NOV11; Ku97]. Naturally, hemodynamic characteristics can act as markers for the diagnosis of a CVD, for evaluating the severity of the condition for therapeutic decision-making and treatment planning and for monitoring.

In the context of CoA, valvular stenosis or myocardial infarction, the drop in blood pressure, related to the resistance the pathology exerts on the flow and thus an increased work load for the left ventricle and/or insufficient blood transport to the organs, is already routinely used as a diagnostic indicator [Bau+09; Bau+10; JW99; Cio+11; Kil11].

The local distribution of the blood pressure can be measured by means of catheterization [Bau+10]. This technique consists in inserting a catheter equipped with a pressure transducer into the vasculature of the patient and maneuvering it, under local anesthesia and guided by fluoroscopy, to the location of interest. Although it is the ‘gold standard’ for pressure quantification, the invasive nature of the method is associated with a risk of complications [Wym+88; Vit+98; Omr+03].

Considerable effort has been put into research on the non-invasive recovery of information on the hemodynamic pressure. The fundamental relationship between the pressure of a fluid and the flow velocity, described by the Navier-Stokes equations (see Section 1.3), permits estimating pressure data from velocity measurements.

Clinical blood flow measurement techniques, however, are limited. To this day, the clinically relevant measurement techniques to assess hemodynamic flow velocities are Doppler echocardiography and phase-contrast magnetic resonance imaging (PC-MRI).

Doppler echocardiography (see Nichols et al. [NOV11, chap. 8] for technical details) is capable of real-time local velocity measurements along a beam or in two-dimensional (2D) planes. It is versatile, non-invasive, free of ionising radiation and can detect relatively small structures, such as leaflets and narrow jets [Kil11]. The main limitation is the restricted access due to limited penetration depth and view angles [Kil11]. In addition, Doppler echocardiography is very user dependent [Bau+10] and measures only velocities aligned with the beam direction.

PC-MRI (see Taylor and Draney [TD04] for a compact and Brown et al. [Bro+14] for an exhaustive introduction) can measure arbitrary velocity components in freely orientable 2D planes or full volumetric flow fields in 3D volumes (also called 4D-Flow) [Mar+12] with no limits to the field of view. The technique is non-invasive and free of ionising radiation and (usually) contrast agents. It is very versatile and can be applied to a vast range of conditions [Kil11]. However, PC-MRI is mainly limited by the image resolution and slice thickness (for 2D PC-MRI), in the clinical practice usually of the order of 2 mm to 3 mm voxel edge length and 2 mm to 10 mm, respectively. The acquisition time of 3D PC-MRI is another severe limitation and has been one of the factors preventing the widespread clinical use of 3D PC-MRI until today. 2D PC-MRI however is a standard and widely available technique, often preferred to Doppler echocardiography as a means of obtaining accurate flow information [HOR08].

The most widespread technique to recover information on the pressure from Doppler echocardiography velocities is the empirical Simplified Bernoulli (SB) formula for CoA and stenosis, a simplification of the Bernoulli equation. SB relates the maximum velocity measured in a narrowing to a pressure difference over the obstruction. However, the formula does not take into account spatial or temporal

patterns in the flow field, nor the geometry of the vessel or shape of the obstruction. As a consequence, the SB formula is known to overestimate the pressure drop [Bau+99; Gar+03; Don+17]. Erbel et al. [Erb+14] consider SB with Doppler velocities unsuitable for pressure drop evaluations.

The abundance of flow information contained in PC-MRI data enables different methods for pressure reconstruction which do not suffer from the limitations of the SB approach. If 3D flow measurements in a complete volume segment are available, the pressure gradient distribution in the domain can be computed ‘directly’ from the velocity images. In this thesis, this approach is called direct pressure estimation. Section 1.4 gives an overview of the methodology. Partial velocity measurements, for instance 2D PC-MRI or Doppler echocardiography, do not cover the complete domain of interest. However, a reconstruction of the volumetric flow field in the blood vessel—including the blood velocity and the relative pressure—can be obtained by means of solving an inverse problem involving the Navier-Stokes equations. The state of the art of this strategy is discussed in Section 1.5.

1.2 Research questions

The topics examined in this thesis are:

1. Analysis the impact of geometric errors on the inverse recovery of the hemodynamic pressure drop and velocity from 2D PC-MRI measurements and development of a model to compensate such errors (Chapter 2).
2. Analysis and validation of new direct pressure gradient estimation techniques, with real in vivo and in vitro 4D flow measurements (Chapter 3).
3. Development and efficient implementation of a reduced order multi-scale model for vascular trees (Chapter 4).

In the remainder of this introduction, the fundamentals of blood flow modelling are discussed, followed by a review of methods of direct pressure estimation and inverse problems in hemodynamics.

1.3 Blood flow modelling

Blood is a suspension of formed elements (i.e., red and white blood cells, platelets) in plasma [BM03]. In hemodynamics—the macroscopic description of the dynamics of blood flow through the vessels—, blood is considered a continuous single-phase fluid (under the continuum hypothesis, cf. Baskurt [Bas07]). Blood acts as a non-Newtonian fluid with viscoelastic behavior, originating from the deformability of

the red blood cells. Its apparent viscosity depends on the viscosity of the plasma (a Newtonian fluid), the hematocrit (volume fraction of blood cells in the blood), red blood cell mechanical properties and red blood cell aggregation [BM03].

Under the continuum hypothesis, blood flow assumed to be governed by the incompressible Navier-Stokes equations,

$$\begin{aligned} \rho \frac{\partial \mathbf{u}}{\partial t} + \rho(\mathbf{u} \cdot \nabla) \mathbf{u} + \nabla p - \nabla \cdot \boldsymbol{\tau} &= \mathbf{0} \\ \nabla \cdot \mathbf{u} &= 0 \end{aligned} \tag{1.1}$$

with the velocity vector $\mathbf{u} : \Omega \times T \mapsto \mathbb{R}^3$, the pressure $p : \Omega \times T \mapsto \mathbb{R}$, in a spatial domain Ω and a time interval T , and neglecting the gravitational force. $\boldsymbol{\tau}$ denotes the viscous stress tensor and is determined by a constitutive equation modeling the shear behavior of blood. Classical models accurately describing the non-Newtonian rheology of blood are the Casson and the Carreau-Yasuda models [Bir87; GvdVJ99]. At high shear rates and moderate to high Reynolds numbers blood behaves approximately as a Newtonian fluid [CK91; Joh+04]. It is often assumed that such conditions exist in the flow through large vessels, on the basis of which blood can be modelled as a Newtonian fluid [TT16]. Under the assumption of a Newtonian fluid, the viscous stress tensor becomes

$$\boldsymbol{\tau} = \mu (\nabla \mathbf{u} + (\nabla \mathbf{u})^\top)$$

with the constant dynamic viscosity, μ . When this assumption is acceptable is a question of on-going debate and it has been shown to be inaccurate in some situations [GvdVJ99].

The arterial system takes an active part in continuously delivering blood at high pressure to the peripheral vasculature [NOV11, p. 77]. In particular, the large arteries deform elastically under increasing blood pressure during systole and act as a reservoir (“Windkessel”) storing blood which is ejected during diastole. Also the long muscular arteries and arterioles actively control the blood propagation to tissue and organs by different mechanisms (see Nichols et al. [NOV11, p. 77]). Hence, for an accurate description of the arterial hemodynamics, it is important to take into account the mechanical properties of the arterial wall tissue. The tissue composition is complex, and in addition to intricate mechanical behavior, involves complex biochemical processes and perfusion. These phenomena, however, are usually neglected in large-scale hemodynamic analyses. In a purely mechanistic setting, the elastic deformation, as a response to forces exerted by the blood flow on the vessel wall, can be accounted for by coupling the Navier-Stokes equations (1.1) with the partial differential equations (PDE) of elasticity with corresponding constitutive laws for the wall deformability. The reader is referred to Sugihara-Seki and Yamada [SY16] for an introduction on the solid mechanics of the arterial wall tissue.

In the practice of computational hemodynamics, computational cost restricts the analysis to small portions of the cardiovascular system, for instance, the section of the vessel containing a stenosis. At the proximal boundary, the inflow velocity profile is usually specified as a boundary condition. At the distal boundary or boundaries,

the feedback of the truncated part of the vasculature can be accounted for by means of lumped network models, see, e.g., Formaggia et al. [FQV09b] for a review of models. Reduced order modelling of the vasculature and vascular trees is a topic of intensive research [PV09]. In Chapter 4 of this thesis, a new multi-scale domain decomposition approach is presented as a contribution to the field.

1.4 Direct pressure gradient estimation

PC-MRI is capable of time-resolved measurements of the 3D velocity field in a 3D volume (called ‘4D-Flow’), containing the vessel of interest. The vessel walls and regions of blood flow are identified by segmentation of the velocity images or from additional anatomic images in order to create a 3D domain of the studied vessel. The domain is usually assumed stationary, i.e., averaged over time, and the time series of measurements associated to the stationary domain. The temporal and spatial resolution of the measurement data allows computing approximately partial derivatives of the data with respect to space and time. By inserting the measured velocities directly into the Navier-Stokes equations (1.1), an approximation of the pressure gradient can be computed directly by evaluating the velocity terms with a suitable numerical method.

Early attempts to reconstruct the relative pressure were presented, for instance, in Urchuk and Plewes [UP94]. The authors invoked the assumption of a Womersley flow and computed the pressure gradient in flow direction from one 2D PC-MR image. Song et al. [Son+94] presented the first 3D approach using the complete Navier-Stokes equations. They recovered velocity data from the pixel intensity displacement of 3D ultra fast CT images and computed the pressure via a Poisson equation, derived by taking the divergence of the Navier-Stokes momentum balance.

This methodology was applied by Yang et al. [Yan+96] to 2D PC-MRI data, who proposed an iterative method for the pressure computation. Tyska et al. [Tys+00] introduced some improvements to the methodology of Yang et al. [Yan+96] and presented the first relative pressure recovery algorithm applied to true 4D-Flow, which was further improved by, e.g., Ebbers et al. [Ebb+02] and Krittian et al. [Kri+12].

Since then, the only studies comparing *in vivo* in CoA patients the relative pressures computed with PPE-based methods with catheterization data were presented by Riesenkampff et al. [Rie+14] and recently, Goubergrits et al. [Gou+19]. In the former study, comparing peak systolic PPE pressure differences with catheterization in 13 patients with moderate AoCo, a slight systematic underestimation was found in average of 1.5 mmHg with a large variability of ± 4.6 mmHg (two standard deviations). The latter study found the PPE method to be sensitive to the image resolution and introduced a minimum requirement for the resolution based on their data (5 voxels/diameter). Furthermore, the PPE method was shown to be sensitive to the lumen segmentation. By eliminating the outermost layer of voxels, the authors achieved a significantly improved match of the PPE estimates with catheterization data. Possible causes are poor boundary data due to partial volume effects and high noise levels,

and the artificial pressure Neumann boundary condition required by the method.

Rengier et al. [Ren+15] validated the PPE method *in vitro* using a phantom consisting of a straight elastic tube with a pulsating flow control and found a good correlation with catheterization data ($r = 0.89$, $p < 0.001$). Other studies validated the PPE using simple phantoms for which the solution is analytically known, e.g., given by a Womersley flow [Ren+14]. These simplified scenarios are a ‘special case’ with weak or negligible convective effects and a lack of complex 3D flow patterns which are characteristic for aortic flow, especially under stenosis, and seem to represent the main challenge for the PPE method in practice.

Several computational fluid dynamics (CFD) studies of the PPE estimator were conducted [Mei+10; Cas+16; Nas+04] for more complex situations, highlighting the shortcomings of the PPE method. The accuracy of the pressure recovery was shown to be sensitive to many factors [Nas+04; Cas+16], such as the image resolution and segmentation, the velocity encoding and turbulence.

Methodological drawbacks of the PPE are the introduction of artificial pressure boundary conditions on the vessel walls and strong regularity requirements for the pressure and the velocity. These restrictions are avoided in an alternative approach, applying a Helmholtz decomposition, rather than the divergence, to the Navier-Stokes equations. This approach leads to a Stokes problem for an auxiliary, non-physical velocity function and the hemodynamic pressure. The methodology was first presented in Cayco and Nicolaides [CN86] in a different context and adapted to relative pressure reconstruction from PC-MRI velocity data by Švihlová et al. [Švi+16]. This technique, the Stokes estimator (STE), was shown in numerical studies to deliver more accurate results than the PPE method [Švi+16; Ber+18b]. In Chapter 3 of this thesis the first comparative study of the STE and the PPE methods using real PC-MRI phantom and patient data is presented in the context of CoA.

Other approaches have been proposed for the computation of averaged pressure differences between two cross-sections of a blood vessel, namely the work-energy relative pressure (WERP) method [Don+15], and its extensions, the virtual WERP (ν WERP) method [Mar+19] and the integral momentum relative pressure (IMRP) estimator [Ber+18b]. A simplification of the WERP method was presented in Donati et al. [Don+17] as a generalization of the Bernoulli approach, which allows to compute the pressure drop from 2D PC-MRI data. These methods are faster to compute than the PPE or the STE, but instead of 3D and time-resolved pressure maps, yield only averaged pressure differences between cross-sections. They are therefore suited to assess the pressure drop, e.g., over a valvular stenosis or CoA, and can be viewed as an alternative for the Doppler echocardiography–simplified Bernoulli approach. The fact that the pressure difference is averaged over the entire cross-section renders the comparison with catheter measurements difficult. The WERP method requires the vessel section of interest not to include any bifurcations (such as the supra-aortic branches), which is avoided by the ν WERP and IMRP methods.

All of the methods depend on the description of the blood flow as the incompressible flow of a Newtonian fluid. The spatial and temporal resolutions at which the underlying Navier-Stokes equations are evaluated are dictated by the PC-MRI

data, i.e., of the order of several millimeters and around 40 ms. As a consequence, these methods do not include the effects of turbulence or non-Newtonian properties of the blood. Furthermore, they do not account for the elastic deformations of the vessel walls. In addition to the model dependency, direct pressure estimation methods are strongly affected by data perturbation, such as noise, image artifacts, the resolution of the data. Noise is an important issue in PC-MRI, where white noise levels of 15 % of the expected maximum velocity are common [Dyv+15], leading to low signal-to-noise ratios (SNR) outside of the peak systole and generally in regions with low flow velocities.

Other approaches estimate the turbulent kinetic energy (TKE) of the flow from the PC-MRI signals [Dyv+06] and propose pressure loss estimators based on the dissipation of the TKE [Dyv+13; Ha+19] as an alternative to the Bernoulli-based formulas. *In vitro* and *in vivo* studies have shown promising results for cases of aortic stenosis [Ha+16b; Ha+19]. The methodology is only applicable to turbulent flow. I.e., pressure drop estimation based on the TKE can be useful for valvular stenosis, where turbulence can be expected, but not for low Reynolds number flows in general, at mild conditions or during diastole.

A drawback of the discussed direct pressure reconstruction methods is the requirement of 3D PC-MRI data¹. To this day, long acquisition times have prevented the translation of 3D PC-MRI to the clinical practice and 3D PC-MRI sequences are rarely available. In addition, in direct methods derived from the Navier-Stokes equations, e.g., Bernoulli-based, PPE, STE, at any instant of time the pressure is uniquely defined up to a constant (with respect to the spatial coordinates). Therefore, only instantaneous pressure differences between different locations can be compared at different times. Catheterization or sphygmomanometer pressure measurements are taken relative to the atmospheric pressure. Hence, the pressures are calibrated with respect to a global reference and pressure values can be compared at different times. A common measure in the clinical practice are the so-called *peak-to-peak* pressure differences, which compare the difference in the pressure maxima registered at different locations during the complete cardiac cycle, thus taking into account time shifts due to the vessel elasticity. Peak-to-peak pressure differences can only be determined by means of catheterization or with the models described above when calibrated with catheterization data, which however invalidates the non-invasiveness of the estimation methods.

1.5 Patient-specific hemodynamics

Increase in computer performance, the advent of PC-MRI and ever improving image quality gave rise to the relatively new research topic of patient-specific hemodynamic simulation of large arteries, based on medical images [TS10].

¹Exceptions are the Bernoulli formula, the simplified advective WERP estimator [Don+17] and early methods which are clinically irrelevant due to their oversimplifications, such as Urchuk and Plewes [UP94].

Patient-specific modelling requires the topology of the patient's vessel under investigation to be reconstructed by segmentation of medical images, e.g., CT or MRI, and a numerical blood flow model to be set up within this domain. The proper inflow and outflow boundary conditions, the initial condition (often neglected) and possibly unknown model parameters have to be calibrated from measurements, for instance, 2D PC-MR images. The determination of the boundary conditions is arguably the most important issue and has received a lot of attention in the literature, which shall be reviewed below. Two different approaches can be distinguished: pre-computation of boundary data directly from PC-MRI data or estimating the required data from the measurements by means of solving an inverse problem. Both approaches are discussed in the subsequent sections.

Solving the model equations, a reconstruction of the hemodynamics (e.g., velocity and pressure fields) with great detail can be obtained from a geometric reconstruction of the vessel and sparse, partial velocity measurements. Since the pressure is (usually) an internal variable of the fluid flow model, pressure drops are readily obtained.

Importantly, a complete hemodynamic characterization can be estimated from partial, 2D PC-MRI measurements. This is a big advantage over direct pressure estimation methods, which with few exceptions² require 3D PC-MRI data. Hence, relative pressure estimation using hemodynamic simulation calibrated with 2D PC-MRI allows to significantly reduce the MRI scan time. This comes at the cost of increased computation times required for the solution of the inverse problem (an optimization problem constrained by the Navier-Stokes equations), compared to direct pressure estimation, where, e.g., only Poisson or Stokes problems have to be solved.

1.5.1 Forward hemodynamic simulations

Inflow and outflow boundary conditions for a CFD model are often determined beforehand from 2D PC-MRI data recorded on slices along the boundaries. A common approach is calculating the mass flow rate by integrating the velocity over the measurement slice at a boundary (i.e., the component in normal direction to the boundary). By temporal interpolation between the images (the time step of the simulation is usually at least one order of magnitude smaller than the temporal resolution of the measurements), the inflow waveform can be obtained. The mass flow rate is a so-called defective boundary condition [For+02], as they do not ensure well-posedness of the flow problem [VV05]. An option is using simplified inflow velocity profiles, such as plug flow, parabolic or Womersley profiles, with time-dependent amplitudes determined by the waveform as Dirichlet boundary conditions [Cam+12].

However, it was demonstrated that helical and retrograde secondary flow patterns are inherent features of the aortic flow, due to the curvature of the aortic arch and the pulsating nature of the flow [Kil+93; Fry+12; Hop+07]. Simplified inflow

²see footnote 1

profiles prevent the development of such features downstream of the boundary and can deteriorate the fidelity of the simulation [TGS17].

In order to account for these complex flow features, some authors used 2D or 3D PC-MRI data directly as Dirichlet boundary conditions by interpolating the velocity measurements onto the computational mesh and simulation time steps. Several studies compared simplified profiles with prescribed mass flow with spatially resolved velocity fields and found that flow patterns in the interior and, for instance the wall shear stress, were sensitive to the inlet boundary condition [Gou+13; Mor+13; Wak+09; Tan+12; Boz+17; Cam+12; Har+13]. However, this approach is limited by the high noise levels and low spatial and temporal resolutions (compared to the numerical discretization) typical for PC-MRI data and possible misalignment of the velocity measurements with the computational domain.

A different approach is enforcing the measured mass flow by means of Lagrange multipliers [For+02; VV05]. This results in an increased computational cost and the need for specialized numerical methods [VV05].

Different strategies exist for personalized outflow boundary conditions. Especially when multiple outflow boundaries are present, the choice of the boundary conditions is not straight forward. Velocity profiles measured with PC-MRI can be prescribed at the outlets, but difficulties arise from possible phase shifts, measurement noise, limited image resolution and the requirement of instantaneous mass conversation [Gal+12]. An alternative present simplified profiles prescribing mass flow waveforms with fixed flow rate ratios between the inlets and outlets determined from PC-MRI measurements or according to cross-section areas if no measurements are available. ‘Zero stress’ homogeneous Neumann conditions can be combined with the former approaches. Windkessel models [For+06; WLW09] and more sophisticated lumped networks [Vig+10; GK08] model the feedback of the truncated vasculature and have been shown to be accurate in complex situations with many outlets [Kim+10; Kun+13; Bar+11; Pir+17; Mor+10]. Usually the model parameters have to be tuned to each specific patient which can be computationally expensive, see Section 1.5.2. A large number of studies uses literature values for the parameters of lumped network models, undermining to some extent the desired ‘patient specificity’. Gallo et al. [Gal+12] compare different popular combinations of outlet boundary conditions for an aortic flow and, while not considering lumped networks, conclude that for accurate results, flow rate boundary conditions based on velocity measurements should be preferred over not fully personalized boundary conditions. Pirola et al. [Pir+17] carried out a similar study of a real aorta, also taking into account three-element Windkessel boundary conditions with empirical parameters. A comparison with different combinations of PC-MRI based mass flow and zero-stress boundary conditions revealed that Windkessel boundary conditions at all outlets were necessary to compute realistic velocity and pressure fields.

The computational domain is reconstructed from anatomical MRI or CT images. However, the segmentation process used to determine the vessel contours is subject to errors caused by the limited image resolution, flow artifacts and partial volume effects [Moo+99]. The impact of errors in the vessel geometry has received rela-

tively little attention. A first recognition of the effect of geometry errors on PC-MRI based flow simulations, in particular regarding the wall shear stress, was presented by Moore et al. [Moo+99] and Moore et al. [MSE97]. Causes of geometric errors and their effects on the arterial blood flow were further investigated in Gambaruto et al. [Gam+08; Gam+11]. The authors found that small changes in geometry cause important variations in the solution. Their work was followed by Sankaran and Marsden [SM11], Sankaran et al. [SGT15b], Sankaran et al. [SGT15a], and Sankaran et al. [San+16], studying geometric uncertainties and other sources of errors in CT-based hemodynamic simulations by means of uncertainty quantification. Again, the results were found to be sensitive to geometric uncertainties. Recently, the issue of geometric errors was investigated theoretically and error bounds were presented [MR19]. All studies concluded that geometric uncertainties have a strong impact on the problem solution. In Chapter 2 of this thesis and in Nolte and Bertoglio [NB19], a method is presented to compensate geometric errors within a data assimilation framework (see the next section).

1.5.2 Inverse problems

Patient-specific model and boundary data required for patient-specific simulations can be estimated from measurements by solving an *inverse problem*. In the present context, the inverse problem takes the form of a PDE-constrained optimization problem.

In contrast to pre-computing the unknown parameters from measurements, for instance by fitting predefined velocity profiles, the optimization approach tunes the parameters such that the discrepancy between the measurements and the model solution is minimized. The parameter adjustment is non-local in the sense that they are calibrated with respect to all available measurements. In general, the measurements are not required to be located at the corresponding boundaries. The inverse approach offers much more versatility regarding the measurement data, the fluid model and estimatable parameters at the expense of higher computational cost.

Formulation and solution methods

The PDE-constrained optimization problems considered here consist of

- a hemodynamic model (the PDE constraint),
- measurements of the model state,
- an observation operator mapping the model state to the observation space,
- an objective function to be minimized, i.e., a measure of the discrepancy between the model predictions and the measurements, weighted by the respective uncertainties.

The task is to estimate uncertain model parameters or the initial condition of the model state by minimizing the objective function.

The model is a system of PDEs that describes the blood flow dynamics as discussed in Section 1.3. In contrast to the direct methods presented in the previous section, this methodology is not limited to the assumption of incompressible flow within a rigid domain. Let us introduce the following short-hand notation for the semi-discrete numerical model, representing a differential algebraic equation (DAE),

$$\dot{X} = \mathcal{A}(X, \theta), \quad (1.2)$$

where $\mathcal{A} : \mathbb{R}^n \times \mathbb{R}^p \mapsto \mathbb{R}^n$ is the model operator and $X(t) \in \mathbb{R}^n$ denotes the model state with n degrees of freedom and an initial condition $X(0)$. Physical model parameters are summarized in the parameter vector $\theta \in \mathbb{R}^p$.

Measurements, $Z(t) \in \mathbb{R}^m$, are related to the state via the observation operator, $\mathcal{H} : \mathbb{R}^n \mapsto \mathbb{R}^m$, such that

$$Z(t) = \mathcal{H}(X) + \zeta, \quad (1.3)$$

where $\zeta \in \mathbb{R}^m$ represents measurement errors, such as noise. This relationship allows *partial* measurements, or measurements of derived quantities of the state, to be used to estimate the state and/or model parameters.

Assuming the initial state X_0 and the parameters θ are sought, a functional can be defined of the form

$$J(X(0), \theta) = \int_{t_0}^T \|Z - \mathcal{H}(X)\|_{W^{-1}}^2 dt + \|X(0) - X_0\|_{C_0^{-1}}^2 + \|\theta - \theta_0\|_{P_0^{-1}}^2, \quad (1.4)$$

with X satisfying the model DAE (1.2). X_0 and θ_0 denote *a priori* expected values for the initial condition and the parameters with their respective uncertainty covariance matrices, C_0 and P_0 . W is the covariance matrix related to the measurement errors.

By minimizing J with respect to $X(0)$ and θ , an optimal trajectory of $X(t)$ can be found (for instance, velocity and pressure fields), balancing the uncertainty of the measurements with the uncertainty of the model predictions. The last two terms in Eq. (1.4) act as regularization terms. Equations (1.2)–(1.4) constitute the typical problem setting of data assimilation (DA), see, e.g., Talagrand [Tal97] and Kalnay [Kal03], and originate from the formulation of a maximum likelihood estimation problem assuming that the measurement noise and the *a priori* parameters have a Normal distribution.

Two classes of methods exist for solving the DA problem described by Eqs. (1.2)–(1.4). *Variational DA*, based on the adjoint of the problem, adjust the complete trajectory of the state $X(t)$, the unknown initial condition $X(0)$ and the unknown parameters θ to the observations given at all times (i.e., ‘past’ and ‘future’ observations). This typically requires computation of the adjoint, repeated forward and backward solves of the problem in an optimization loop and storing the complete time history of the state. The complexity, i.e., number of iterations, is independent on the number of parameters. Applying adjoint-based methods to joint state–parameter estimation

in realistic problems (i.e., 3D, time-dependent, nonlinear) is challenging due to the large requirements in computational power, but routinely done in numerical weather prediction [Kal03] using large computing clusters.

Sequential DA assimilates observations into the model state, once they are ‘encountered’, directly during the time integration of the forward problem. Sequential methods are recursive and optimize state and parameters at a point in time with respect to all past observations, but do not consider future observations. In advantages with respect to variational DA are that storage of the state is not required and that gradients of the functional J and adjoints are avoided (‘derivative-free’ optimization). On the other hand, the complexity increases with the number of parameters. Sequential DA methods are often extensions of the linear Kalman filter, such as the Ensemble Kalman Filter [Eve09] (EnKF) or the Unscented Kalman Filter [JU97] (UKF). The main challenge of the Kalman filtering approaches is that the covariance matrix of the uncertainties, a dense square matrix of the size of the dimension of the uncertain parameters and/or initial condition, has to be propagated in time with the model. Instead, an ensemble of states (‘particles’) can be used to approximate the error covariance matrix. This is achieved in the UKF and the EnKF, using deterministic or stochastic particles, respectively. Sequential DA methods are prohibitive for state estimation in realistic hemodynamic problems if no assumptions are made to severely reduce the problem size. The large number of particles required (for instance, 50 to 100 for the EnKF) results in a high demand in CPU time, since for each particle one independent forward problem has to be solved. These particle forward problems can be solved simultaneously on a parallel computer.

Joint state–parameter estimation in hemodynamics

In hemodynamics, Funke et al. [Fun+19] used variational DA (4D-Var) to reconstruct the flow in a patient-specific aneurysm from PC-MRI data. Using a coarse numerical mesh and large time steps, the computational time was reported to be 50 to 100 times that of the forward problem. Since even the accurate forward solution of the Navier-Stokes equations in the convection-dominated or turbulent flow regime is a challenging task, full-scale variational DA is still out of reach for state estimation in aortic flow simulations.

Both the UKF and the EnKF have been used successfully for low-order hemodynamic models. In Pant et al. [Pan+14], patient-specific hemodynamics in an aorta with CoA were computed with a multi-scale approach, where the parameters of lumped models for the boundary conditions of the full-dimensional fluid problem were estimated in a 0D surrogate model by means of the UKF. DeVault et al. [DeV+08] used the EnKF to determine the boundary conditions of a 1D representation of the blood flow through a vascular network from Doppler echocardiography velocity measurements.

Parameter estimation in hemodynamics

The data assimilation problem can be greatly simplified by neglecting the uncertainty in the initial condition of the state (number of unknowns of the order 10^5 to 10^7) and only considering uncertainties in the parameters (typically dozens or less), describing, i.e., boundary conditions and material properties.

Both variational and sequential DA methods are applicable to the resulting parameter estimation problem. For small numbers of parameters, the sequential approach offers the advantages of computational efficiency (mostly due to the recursivity) and implementational simplicity.

A reduced order version of the UKF for parameter estimation was presented in Moireau and Chapelle [MC11], referred to as the Reduced-Order Unscented Kalman Filter (ROUKF). The number of particles it employs is the number of parameters to be estimated plus one. The ROUKF has been used successfully in hemodynamic applications, namely, parameter identification in fluid–structure interaction problems [Moi+13; BMG12; Ber+14] and in reduced order models of the arterial network [Lom14; Cai+17; MCB18]. It was furthermore employed in Chapter 2 of this thesis and in Nolte and Bertoglio [NB19] for parameter estimation in a CFD study of arterial blood flow, using a geometric errors compensating wall boundary model. Lal et al. [LMN17] used the EnKF for parameter estimation in a cardiovascular network.

Sequential data assimilation is not suitable for estimating complex velocity inflow profiles because of the high number of degrees of freedom to be determined (of the order of hundreds or thousands).

Variational data assimilation was used for the boundary parameter estimation problem in, for instance, Formaggia et al. [FVV08], who extended the treatment of defective boundary conditions presented in Veneziani and Vergara [VV05]. In synthetic 2D and axisymmetric studies of blood flow, assuming a steady state—hence avoiding the issue of uncertain initial conditions—, D’Elia et al. [DPV12] estimated Neumann boundary condition data from artificial velocity measurements using variational data assimilation. The approach was extended in Tiago et al. [TGS17] to the estimation of full 3D inflow velocity profiles from partial velocity data given at slices in different locations. In contrast to the assumption of simplified velocity profiles, helical and secondary flow patterns could be recovered downstream from the inlet. Guerra et al. [Gue+18] presented a further extension to non-Newtonian blood flow. A similar procedure was presented in Koltukluoğlu and Blanco [KB18], also assuming stationary flow, for estimating the velocity inflow profile from 4D-Flow data. The methodology delivered accurate results in an experiment using real data acquired in an aortic phantom.

An adjoint-based parameter estimation method was presented in Ismail et al. [IGW12; IWG13] and applied to real patient-specific aortic flow problems, considering both a CFD setting and coupling the hemodynamics to the elastic vessel wall mechanics. Windkessel parameters were calibrated from flow rate and pressure measurements. The method proved robust and delivered realistic results.

State observers in hemodynamics

A different approach to state estimation consists in using state observers, which add a feedback term with a constant and sparse precomputed gain matrix to the model equations, involving the discrepancy between observations of the state and the measurements (see, e.g., Heys et al. [Hey+10], Funamoto et al. [Fun+08], and Bertoglio et al. [Ber+13]). This methodology is effective for estimating the state in presence of uncertainties in the initial guess but estimating model parameters is not possible.

However, sequential data assimilation methods for parameter estimation can be combined with state observers in order to enable computationally inexpensive joint state/parameter estimation. See, e.g., Moireau et al. [Moi+13] for applications in hemodynamics, where the observer was used in the context of joint estimation of the state and boundary tissue support parameters.

1.6 Thesis overview

This thesis contributes to the areas of patient-specific inverse hemodynamics, direct pressure gradient estimation and multi-scale modeling of vascular networks.

Patient-specific inverse hemodynamics: Geometric uncertainty in image-based vessel reconstructions is known to be an important issue in patient-specific simulations. Chapter 2 assesses in a synthetic test case of coarctation of the aorta the impact of geometry errors on the pressure drop obtained from velocity measurements by means of sequential data assimilation. A boundary model and a numerical method capable of compensating such errors is presented. While the issue of inflow and outflow boundary conditions has received a lot of attention, to the best of the author’s knowledge, no previous studies have presented a method to reduce geometric errors in the vessel wall. However, virtually all studies based on the Navier-Stokes equations use computational domains obtained from imaging, unavoidably affected by uncertainty.

Direct pressure gradient estimation: 4D-Flow based pressure gradient estimation techniques have been widely used in proof-of-concept studies for the last two decades, however they are not routinely used in the clinical practice. Only few studies compared pressure drop estimators with catheterization. In Chapter 3, a comparison of the PPE and the STE pressure gradient estimation methods with pressure catheterization measurements is presented for aortic phantoms and CoA patients. To the best of the author’s knowledge, this is the first time that the STE method is validated using real data. The impact of image resolution and lumen segmentation—strongly related to the geometric errors discussed in the previous paragraph—is investigated.

Multiscale modeling of vascular networks: The method of asymptotic partial decomposition of a domain (MAPDD), a new multiscale method, describes vascular trees as networks of full-dimensional junctions in which the flow is gov-

erned by the Navier-Stokes equations, connected by vessels in which the flow is assumed to be of Womersley type. Chapter 4 discusses a practical implementation of the MAPDD and validates the theory with numerical examples.

